SUPPLEMENTARY MATERIAL FOR:

Initiating or Switching to Insulin Degludec/Insulin Aspart in Adults with Type 2 Diabetes: a Real-world, Prospective, Non-interventional Study across Six Countries

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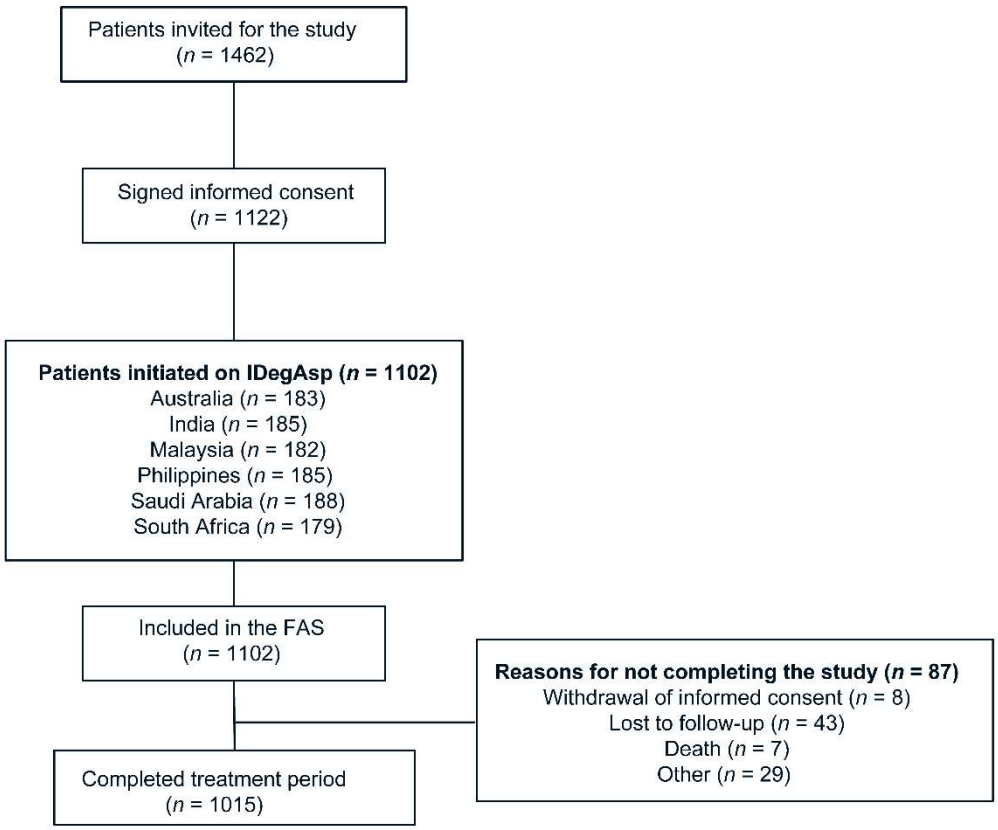
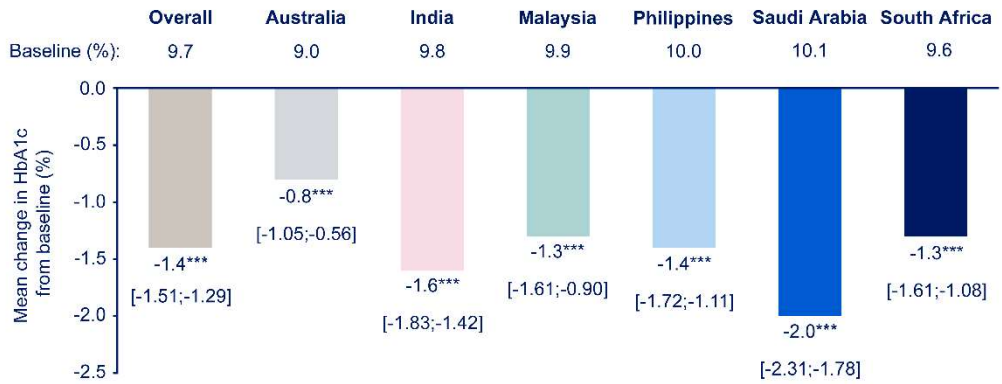
Figure S1. Patient flow through the study.



FAS, full analysis set; IDegAsp, insulin degludec/insulin aspart; *n*, number of participants

Figure S2. Change in HbA1c from baseline to EOS by country subgroup.



***$P < 0.0001$.

Data are mean [95% CI]. Baseline data are for participants contributing to the analysis. The full adjusted model included baseline value, time, time squared of HbA1c measure, age, sex, BMI, previous antidiabetic treatment regimen, and study site. To handle (quadratic) deviation from linearity, a random coefficient model with time and time squared as fixed coefficients, and patient and patient time as random coefficients was used. An unstructured covariance matrix was used to describe the variability for repeated measurements.

BMI, body mass index; CI, confidence interval; EOS, end of study

Table S1. List of independent ethics committees/institutional review boards who approved the study

Country	Name of independent ethics committee/institutional review boards
Australia	Northern Sydney Local Health District Human Research Ethics Committee, New South Wales
	Bellberry Human Research Ethics Committee, Adelaide
India	Institutional Ethics Committee FORTIS Hospital, Mohali
	Max Healthcare Ethics Committee, New Delhi
	AMRI Hospitals Institutional Ethics Committee, Bhubaneswar
	People Tree Hospitals Ethics Committee, Karnataka
	Institutional Ethics Committee Columbia Asia Hospitals, Bangalore
	Dew and Trinity Institutional Ethics Committee, Maharashtra
	Universal Ethics Committee – a Unit of Aurous Healthcare Research and Development India Private Limited, Chennai
	Institutional Ethics Committee Fortis Hospital Shalimar Bagh, New Delhi
	Narayana Superspeciality Hospital Ethics Committee, Howrah
	Institutional Ethics Committee, Excelcare Hospitals, Guwahati
Malaysia	Medical Research and Ethical Committee, Ministry of Health Malaysia, Shah Alam
	Independent Ethics Committee, Ramsay SimeDarby Health Care, Shah Alam
	Jawatankuasa Etika Penyelidikan Manusia Human Research Ethic Committee Universiti Sains Malaysia (HREC), Kelantan
Philippines	Manila Doctors Hospital Institutional Review Board, Manila

	University of Santo Tomas Hospital Research Ethics Committee, Manila
	Makati Medical Center Institutional Review Board, Makati City
	Davao Doctors Hospital - Institutional Review Board, Davao City
	St Luke's Medical Center - Institutional Ethics Review Committee, Quezon City
	University of the East Ramon, Magsaysay Memorial Medical Center, Inc. Research Institute for Health Sciences Ethics Review Committee, Quezon City
	Perpetual Succour Hospital Institutional Ethics and Review Board, Cebu City
Saudi Arabia	King AbdulAziz University Faculty of Medicine Research Ethics Committee, Jeddah
	Institutional Review Board King Fahad Medical City, Riyadh
	King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs, Riyadh
	Specialized Medical Center Hospital Institutional Review Board, Riyadh
South Africa	Pharma - Ethics Independent Research Ethics Committee, Centurion

Table S2. Summary of endpoints analysed using the on-treatment observation period.

	Observed mean (SD) at baseline		Estimated mean (SE) at EOS		Estimated difference (baseline to EOS) [95% CI]
HbA1c, %	9.7 (1.95)		8.3 (0.05)		–1.4 [–1.52;–1.30]; *P* < 0.0001
FPG, mmol/L	10.9 (4.07)		8.2 (0.14)		–2.7 [–2.96;–2.42]; *P* < 0.0001
Body weight, kg	79.6 (19.15)		79.3 (0.26)		–1.0 [–1.50; –0.50]; *P* < 0.0001
	n	***n* with event**	**Events**	**Rate**	**Estimated rate ratio [95% CI]**
Hypoglycaemic episodes					
Non-severe					
Within 4 weeks prior to initiation	1038	128	364	4.57	0.47 [0.31;0.73]; *P* = 0.0007
Within 4 weeks prior to EOS or discontinuation	973	44	162	2.17	
Nocturnal non-severe					
Within 4 weeks prior to initiation	1038	59	142	1.78	0.23 [0.12;0.44]; *P* < 0.0001
Within 4 weeks prior to EOS or discontinuation	973	14	31	0.42	
Severe					
Within 26 weeks prior to initiation	1058	23	51	0.10	0.06 [0.02;0.25]; *P* < 0.0001
Within 26 weeks prior to EOS	976	3	3	0.01	

Data based on the FAS. Negative binomial regression models specifying a log-transformed follow-up time offset term was used to examine the incidence rate of hypoglycaemic events occurring prior to initiation of IDegAsp and prior to EOS or at discontinuation.

CI, confidence interval; EOS, end of study; FAS, full analysis set; FPG, fasting plasma glucose; IDegAsp, insulin degludec/insulin aspart; *n*, number of participants contributing to the analysis; rate, events per patient-year; SD, standard deviation; SE, standard error

Table S3. Demographic and clinical characteristics at baseline by country.

	Overall ***N*** **= 1102**	**Australia** ***N*** **= 183**	**India** ***N*** **= 185**	**Malaysia** ***N*** **= 182**	**Philippines** ***N*** **= 185**	**Saudi Arabia** ***N*** **= 188**	**South Africa** ***N*** **= 179**
Age, mean (SD)	58.6 (12.23)	67.2 (10.92)	58.1 (10.28)	56.4 (11.88)	58.5 (12.21)	54.8 (12.23)	56.5 (11.73)
Male	591 (53.6)	118 (64.5)	106 (57.3)	95 (52.2)	74 (40.0)	116 (61.7)	82 (45.8)
Duration of diabetes (years), mean (SD)	13.3 (8.33)	19.0 (8.74)	14.4 (8.08)	11.2 (7.99)	10.8 (7.25)	11.6 (7.82)	12.6 (7.16)
Body weight (kg), mean (SD)	79.5 (19.56)	93.0 (20.61)	70.1 (11.91)	71.8 (14.38)	67.1 (14.11)	85.3 (16.44)	90.5 (20.86)
BMI (kg/m^2), mean (SD)	29.2 (5.86)	31.6 (5.04)	26.5 (3.90)	27.4 (4.62)	26.0 (5.28)	31.2 (5.56)	32.7 (6.62)
HbA1c (%), mean (SD)	9.8 (1.99)	9.1 (1.82)	9.7 (1.80)	10.0 (2.14)	10.2 (2.08)	10.1 (1.98)	9.6 (1.89)
FPG (mg/dL), mean (SD)	198.0 (75.97)	165.1 (58.87)	187.4 (66.84)	198.5 (79.19)	208.0 (84.06)	207.7 (66.54)	202.0 (85.99)
Antidiabetic treatment, *n* (%)							
OADs only	371 (35.1)	27 (14.8)	90 (50.0)	52 (31.5)	83 (48.0)	76 (42.9)	43 (24.0)
Premix insulin ± bolus insulin (± OADs)	232 (21.9)	45 (24.6)	35 (19.4)	36 (21.8)	18 (10.4)	32 (18.1)	66 (36.9)
Basal insulin only (± OADs)	230 (21.8)	59 (32.2)	19 (10.6)	38 (23.0)	57 (32.9)	33 (18.6)	24 (13.4)
Basal–bolus insulin (± OADs)	137 (13.0)	20 (10.9)	32 (17.8)	24 (14.5)	11 (6.4)	15 (8.5)	35 (19.6)
GLP-1 RA ± insulin (± OADs)	87 (8.2)	32 (17.5)	4 (2.2)	15 (9.1)	4 (2.3)	21 (11.9)	11 (6.1)

Daily dose of previous prandial insulin (U), mean (SD)	25.8 (22.84)	22.7 (13.45)	26.2 (19.18)	27.0 (22.05)	24.6 (21.19)	24.2 (21.45)	27.9 (30.43)
Medical history and diabetes complications, *n* (%)							
Number of subjects	876	178	156	160	128	95	159
Cardiovascular disease	150 (17.1)	51 (28.7)	23 (14.7)	27 (16.9)	12 (9.4)	13 (13.7)	24 (15.1)
Peripheral vascular disease	15 (1.7)	10 (5.6)	0	1 (0.6)	4 (3.1)	0	0
Diabetic retinopathy	102 (11.6)	49 (27.5)	6 (3.8)	20 (12.5)	12 (9.4)	2 (2.1)	13 (8.2)
Diabetic neuropathy	216 (24.7)	61 (34.3)	33 (21.2)	46 (28.8)	35 (27.3)	16 (16.8)	25 (15.7)
Diabetic nephropathy	178 (20.3)	48 (27.0)	17 (10.9)	64 (40.0)	24 (18.8)	7 (7.4)	18 (11.3)

BMI, body mass index; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic drug; *N*, number of participants in the full analysis set; SD, standard deviation; U, unit

Table S4. Reasons for discontinuing IDegAsp treatment during the study period.

	Overall *n* = 59
Change in coverage status disfavouring IDegAsp	10 (16.9)
Adverse event	5 (8.5)
Unacceptable hypoglycaemia profile/pattern	2 (3.4)
Lack of convenience	2 (3.4)
Insufficient effect on glycaemic control	2 (3.4)
Pregnancy or intentions to become pregnant	2 (3.4)
Weight gain	0
Other	32 (54.2)
Unknown	4 (6.8)

Data are number of participants (%). Analysed using the on-treatment observation period. A change in coverage status disfavouring IDegAsp refers to a change in healthcare insurance or reimbursement requirements that led to worse access to the drug.

IDegAsp, insulin degludec/insulin aspart; *n*, number of participants with a response

Table S5. Healthcare resource utilisation.

	n	*n* with events	Events	Rate	Estimated rate ratio [95% CI]
HRU associated with diabetes and its complications					
Self-reported outpatient visits					
Within 12 weeks prior to initiation	1065	394	1248	5.10	0.44 [0.35;0.54]; *P* < 0.0001
Within 12 weeks prior to EOS or discontinuation	974	197	498	2.23	
Self-reported emergency room visits					
Within 12 weeks prior to initiation	1064	46	60	0.25	0.22 [0.11;0.44]; *P* < 0.0001
Within 12 weeks prior to EOS or discontinuation	972	9	12	0.05	
Self-reported other healthcare provider visits and contacts outside of the hospital setting (face-to-face, telephone and email)					
Within 12 weeks prior to initiation	1063	169	412	1.69	0.84 [0.64;1.11]; *P* = 0.2286
Within 12 weeks prior to EOS or discontinuation	972	156	317	1.42	
Self-reported work days missed					
Within 12 weeks prior to initiation	1027	58	505	2.14	0.06 [0.03;0.14]; *P* < 0.0001
Within 12 weeks prior to EOS or discontinuation	909	9	28	0.13	
Self-reported in-patient hospitalisations					
Within 12 weeks prior to initiation	1065	78	90	0.37	0.24 [0.14;0.41]; *P* < 0.0001
Within 12 weeks prior to EOS or discontinuation	972	12	20	0.09	
HRU associated with severe hypoglycaemia					
Self-reported outpatient visits					
Within 26 weeks prior to initiation	1027	83	272	0.53	0.70 [0.44;1.12]; *P* = 0.1343

Within 26 weeks prior to EOS or discontinuation	912	65	168	0.37	
Self-reported emergency room visits					
Within 26 weeks prior to initiation	1027	15	18	0.04	0.19 [0.05;0.70]; *P* = 0.0124
Within 26 weeks prior to EOS or discontinuation	910	3	3	0.01	
Self-reported in-patient hospitalisations					
Within 26 weeks prior to initiation	1027	12	16	0.03	0.21 [0.05;0.83]; *P* = 0.0262
Within 26 weeks prior to EOS or discontinuation	910	3	3	0.01	
Self-reported episodes requiring assistance from an ambulance					
Within 26 weeks prior to initiation	1027	7	8	0.02	0.14 [0.02;1.22]; *P* = 0.0749
Within 26 weeks prior to EOS or discontinuation	910	1	1	0.00	
Self-reported episodes required administration of glucagon					
Within 26 weeks prior to initiation	1027	2	3	0.01	1.13 [0.11;11.76]; *P* = 0.9162
Within 26 weeks prior to EOS or discontinuation	910	2	3	0.01	
Self-reported work days missed					
Within 26 weeks prior to initiation	1025	7	46	0.09	0.10 [0.01;0.76]; *P* = 0.0261
Within 26 weeks prior to EOS or discontinuation	902	3	4	0.01	
Self-reported other healthcare provider visits and contacts outside of the hospital setting (face-to-face, telephone, and email)					
Within 26 weeks prior to initiation	1026	19	57	0.11	0.88 [0.39;1.98]; *P* = 0.7494
Within 26 weeks prior to EOS or discontinuation	910	25	42	0.10	

Data based on FAS. Negative binomial regression models specifying a log-transformed follow-up time offset term were used to examine the incidence rate of self-reported resource utilisation occurring prior to initiation of treatment with IDegAsp and prior to EOS or discontinuation.

IDegAsp, insulin degludec/insulin aspart; CI, confidence interval; EOS, end of study; FAS, full analysis set; HRU, healthcare resource utilisation; *n*, number of participants contributing to the analysis; rate, events per patient-year

Table S6. Adverse events.

	Serious			Non-serious		
	n	**%**	**E**	***n***	**%**	**E**
Adverse events	39	3.5	57	68	6.2	115
Severity						
Mild	9	0.8	15	58	5.3	98
Moderate	16	1.5	20	15	1.4	17
Severe	19	1.7	22	0		
Causality						
Probable	1	0.1	2	15	1.4	23
Possible	2	0.2	2	13	1.2	16
Unlikely	31	2.8	45	42	3.8	72

Data based on full analysis set.

%, percentage of participants; E, number of events; *n*, number of participants